Combination of Neural Inverse Optimal Control with a Kernel-Based Regularization Learning Algorithm to Prevent Hypoglycemia in Type 1 Diabetes Patients

Blanca S. Leon[1], Valeriya Naumova[2], Eduardo Ruiz-Velazquez[3], Andrew D. McCulloch[1], Edgar N. Sanchez[4]

Abstract— **Hypoglycemia periods in Type 1 Diabetes mellitus (T1DM) patients are a dangerous condition leading to serious acute complications, such as diabetic coma or death. Despite recent technological and scientific advances in T1DM therapy management, prevention of severe hypoglycemic periods still remains a challenge.**

In this paper, we present a novel combination of a neural inverse optimal control via control Lyapunov function (CLF) combined with a kernel-based regularization learning predictive algorithm (KAR) for optimal control of the blood glucose levels with a strong focus on timely detection and prevention of acute debilitating and harmful hypoglycemic events. We describe how the proposed scheme can be used for aforementioned problem and report the results of the tests on University of Virginia (UVA)/Padova Simulator as well as comparing them with existing literature. The performance assessment of the algorithms has been made with the use of control variability grid analysis (CVGA).

I. Introduction

According to the International Diabetes Federation, diabetes mellitus is one of the costliest health problems in the world and one of the major causes of death worldwide. Prevalence of diabetes mellitus in 2013 was 387 million people worldwide and is expected to increase by 205 million people before 2035. Diabetes caused 4.9 million deaths in 2014 and the estimated global healthcare expenditures to treat and prevent diabetes and its complications reached $612 billion (US). Type 1 diabetes mellitus (T1DM) is a chronic auto-immune disease caused by a lack of insulin due to the destruction of insulin-producing beta cells in the pancreas [1]. Although insulin was discovered in 1921, the ability of insulin to promote glucose utilization and glycogen formation was established in 1926 [2]. For many years, the correlation between the degree of hyperglycemia and the severity of chronic complications was the major quest. The Diabetes Control and Complication Trial, the most important study of glycemic control in the field of Diabetes, demonstrated that glycemic control with continuous insulin infusion in T1DM patients can reduce or delay long-term complications associated to hyperglycemia such as cardiovascular disease, nephropathy, neuropathy, amputation and retinopathy, nevertheless, with this intense insulin therapy a threefold increase in short term complications related to severe hypoglycemia was detected [3]. There is also a longer term complication of frequent and severe hypoglycemia which is hypoglycemia unawareness [4].

Keeping blood glucose within normal bounds has become the daily challenge for T1DM patients. Common insulin therapy consists in providing insulin to the patient subcutaneously [5] [3]. In 2012, the Food and Drug Administration (FDA) published a guidance, which pointed out the basic device parts of the so called Artificial Pancreas Device System (APDS). Consisting of: 1) a continuous glucose monitor (CGM) with a Blood Glucose Device (BGD) to optimize the measures of the CGM, 2) a continuous subcutaneous insulin infusion (CSII) pump, 3) a control algorithm which calculates the adequate insulin dose for the patient [6].

Different control techniques have been applied for T1DM closed-loop control *in silico* and *in vivo* testing. These schemes include the classical PID control scheme [7], [8], [9], [10], [11], [12], MPC (model predictive control) [7], [13], [14], [15], [16], [17], [18] MPILC (a combination of iterative learning control and MPC) [19], adaptative control [20], linear robust μ-synthesis control [21], H_∞ - based control [22], [23]. In this paper, a control technique based on discrete-time inverse optimal control via a control Lyapunov function (CLF) for nonlinear systems trajectory tracking is used to compute insulin infusion for T1DM patients [24]. A kernel-based regularization-learning algorithm [25] is incorporated in the controller as a predictor to prevent the risk of hypoglycemia. Control-variability grid analysis (CVGA) presented in [26] is used as a tool to present the simulation results. The UVA/Padova Type 1 Diabetes Mellitus Simulator (T1DMS) is used to test the proposed controller [27], [8].

T1DMS and its distributed version can be obtained through the UVA/Padova organization, enhanced by models

[1] Department of Bioengineering, University of California San Diego, La Jolla, CA, USA

[2] Simula Research Laboratory, Norway, e-mail: valeriya@simula.no

[3]CUCEI, Universidad de Guadalajara, Av. Revolucion No. 1500, C.P. 44430, Guadalajara, JAL, Mexico, e-mail: eduardo.ruiz@cucei.udg.mx

[4]CINVESTAV, Unidad Guadalajara, Apartado Postal 31-438, Plaza La Luna, Guadalajara, Jalisco, C.P. 45091, Mexico.

of subcutaneous (s.c.) insulin pumps and glucose monitors. The aforementioned distributed version has a cohort of 30 virtual patients (10 adults, 10 adolescents, 10 children). It also adds models of continuous glucose monitoring (CGM) and s.c. insulin delivery, which allows more realistic simulations. Furthermore, this system has been accepted by the FDA as a substitute to animal trials in pre-clinical testing of closed-loop control strategies. Several strategies for blood glucose regulation in T1DM have been designed and/or tested using T1DMS and analyzed with CVGA. Next, a few of these approaches are briefly described.

In [28] the authors present a control scheme using a patient-specific H_∞ robust controller to reduce the risks of hyperglycemia and hypoglycemia. The scheme is further enhanced by an Insulin Feedback Loop (IFL) and a Safety Mechanism (SM) to reduce the risks of hyperglycemia and hypoglycemia in T1DM.

The control scheme is tested on T1DMS using the data from 101 adults. Using the CVGA as a performance assessment metrics, the controller illustrates satisfactory results with a slight tendency towards hyperglycemia.

A personalized insulin infusion advisory system (IIAS) is proposed in [29] to provide real-time estimations of insulin infusion rate for T1DM patients. The approach consists, 1) a personalized model based on the combined use of CMs and an RNN for the simulation of glucose-insulin metabolism and 2) an automatic algorithm for the on-line adaptation of NMPC parameters. First, using data corresponding to 5 days of open-loop experiments of *in-silico* subjects were performed to train glucose-insulin metabolism models. After the 5 days of the tuning, IIAS has been set up and its performance has been tested on data of 10 adult patients from T1DMS. The performance results for IIAS were similar to those for the controller scheme, i.e., a benign error and a slight tendency towards hypoglycemia.

Model Predictive Control equipped with an asymmetric quadratic cost function, postprandial input integral and postprandial output soft constraints are presented in [30]. The controller was synthesized with a linear glucose-insulin model customized on the basis of the patient clinical knowledge. T1DMS is used to perform a perturbed scenario in which the controller is not aware of random variations of insulin sensitivity in 100 adult virtual patient. For both scenarios the performance evaluation results using CVGA are quite similar; whereas for the perturbed scenario some error is observed.

In this paper, demonstrating the effectiveness of the control scheme along with the predictor, we consider three different simulation trials: 1. Using bolus after meals without controller for five days (10 patients), 2. Using the controller for five days (10 patients), 3. Using the controller and the predictor together for five days (10 patients).

This paper is organized as follows: First the inverse optimal control strategy via CLF and the neural model are described; then the kernel-based regularization-learning algorithm is presented, followed by simulation results where three different scenarios are tested using the UVA/Padova simulator, these results are presented using CVGA. Finally, conclusions are presented.

II. Discrete Time Non-linear Systems Inverse Optimal Control Via CLF

As described by Leon et al. [24], when we deal with optimal control, the solution of the Hamilton-Jacobi-Bellman (HJB) partial differential equation is required. A control law as a result of the optimal control formulation and the associated HJB solution provides stability, optimality and robustness with respect to disturbances [31]. However, determining a solution for the HJB equation is the main drawback of the optimal control; this solution may not exist or may be extremely difficult to obtain. An inverse optimal control approach for a class of discrete-time nonlinear systems is used, which does not require a solution of the HJB equation and guarantees robust stability in the presence of disturbances and the minimization of a meaningful cost functional. A quadratic candidate CLF is used to synthesize the inverse optimal control law.

Considering a nonlinear affine system

$$x_{k+1} = f(x_k) + g(x_k)\, u_k \qquad x_0 = x(0) \tag{1}$$

where $x \in \Re^n$ which is the state of the system at time $k \in \mathcal{N}$, $u \in \Re^m$ $f : \Re^n \to \Re^n$, $g : \Re^n \to \Re^{n\times m}$, are smooth and bounded mappings, $f(0) = 0$, $\mathcal{N}$ denotes the set of nonnegative integers. The following meaningful cost functional is associated with the trajectory tracking problem for system (1)

$$C(z_k) = \sum_{n=k}^{\infty} \left(l(z_n) + u_n^T R(z_n)\, u_n \right) \tag{2}$$

where $z_k = x_k - x_{\delta,k}$ with $x_{\delta,k}$ as the desired trajectory for x_k; $z_k \in \Re^n$; $C(z_k) : \Re^n \to \Re^+$; $l(z_k) : \Re^n \to \Re^+$ is a positive semi-definite function and $R(z_k) : \Re^n \to \Re^{m\times m}$ is a real symmetric positive definite weighting matrix. The entries of $R(z_k)$ can be fixed or can be functions of the system state in order to vary the weighting on control efforts according to the state value [32]. Considering the state feedback control design problem, we assume that the full state x_k is available. Using the optimal value function $C^*(x_k)$ for (2) as Lyapunov function $V(x_k)$, equation (2) can be rewritten as

$$\begin{aligned} V(z_k) &= l(z_k) + u_k^T R(z_k)\, u_k \\ &\quad + \sum_{n=k+1}^{\infty} \left(l(z_n) + u_n^T R(z_n)\, u_n \right) \\ &= l(z_k) + u_k^T R(z_k)\, u_k + V(z_{k+1}) \end{aligned}$$

where it is required the following boundary condition $V(0) = 0$ so that $V(z_k)$ becomes a Lyapunov function. From the Bellman optimality principle [33] [34], it is known that, for the infinite horizon optimization case, the value

function $V(z_k)$ becomes time invariant and satisfies the discrete-time (DT) Bellman equation [34] [35] [36]

$$V(z_k) = \min_{u_k} \left\{ l(z_k) + u_k^T R(z_k) u_k + V(z_{k+1}) \right\}$$

where $V(z_{k+1})$ depends on both z_k and u_k by means of z_{k+1} in (1). Note that the DT Bellman equation is solved backward in time [36].

In order to establish the conditions that the optimal control law must satisfy, we define the discrete-time Hamiltonian $H(z_k, u_k)$ as

$$H(z_k, u_k) = l(z_k) + u_k^T R(z_k) u_k + V(z_{k+1}) - V(z_k) \quad (3)$$

A necessary condition that the optimal control law should satisfy is $\frac{\partial H(z_k, u_k)}{\partial u_k} = 0$, then

$$\begin{aligned} 0 &= 2R(z_k) u_k + \frac{\partial V(z_{k+1})}{\partial u_k} \\ &= 2R(z_k) u_k + \frac{\partial z_{k+1}}{\partial u_k} \frac{\partial V(z_{k+1})}{\partial u_k} \\ &= 2R(z_k) u_k + g^T(x_k) \frac{\partial V(z_{k+1})}{\partial u_k} \end{aligned}$$

Therefore, the optimal control law to achieve trajectory tracking is formulated as

$$u_k^* = -\frac{1}{2} R^{-1}(z_k) g^T(x_k) \frac{\partial V(z_{k+1})}{\partial z_{k+1}}$$

with the boundary condition $V(0) = 0$. For solving the trajectory tracking inverse optimal control problem, it is necessary to solve the following HJB equation:

$$\begin{aligned} & l(z_k) + V(z_{k+1}) - V(z_k) \\ & + \frac{1}{4} \frac{\partial V^T(z_{k+1})}{\partial z_{k+1}} g^T(x_k) R^{-1}(z_k) g^T(x_k) \frac{\partial V(z_{k+1})}{\partial z_{k+1}} \\ & = 0 \end{aligned} \quad (4)$$

which is a challenging task. To overcome this problem, we propose to use the inverse optimal control approach.

Definition 1 Consider the tracking error as $z_k = x_k - x_{\delta,k}$, being $x_{\delta,k}$ the desired trajectory for x_k. The control law

$$u_k^* = -\frac{1}{2} R^{-1}(z_k) g^T(x_k) \frac{\partial V(z_{k+1})}{\partial z_{k+1}}, \quad (5)$$

will be inverse optimal (globally) stabilizing along the desired trajectory $x_{\delta,k}$ if:

(i) It achieves (global) asymptotic stability of $x_k = 0$ for system (1) along reference $x_{\delta,k}$;

(ii) $V(z_k)$ is (radially unbounded) positive definite function such that the inequality

$$\overline{V} := V(z_{k+1}) - V(z_k) + u_k^{*T} R(z_k) u_k^* \leq 0$$

is satisfied

Selecting $l(z_k) := -\overline{V}$, then $V(z_k)$ is a solution for (4) and cost functional (2) is minimized.

As established in *Definition 1*, the inverse optimal control law for trajectory tracking is based on the knowledge of $V(z_k)$. Then, a CLF $V(z_k)$ is proposed, such that (i) and (ii) are guaranteed. Hence, instead of solving (4) for $V(z_k)$, a quadratic candidate CLF $V(z_k)$ for (5) is proposed with the form:

$$V(z_k) = \frac{1}{2} z_k^T P z_k \qquad P = P^T > 0 \quad (6)$$

in order to ensure stability of the tracking error z_k, where

$$\begin{aligned} z_k &= x_k - x_{\delta,k} \\ &= \begin{bmatrix} (x_{1,k} - x_{1\delta,k}) \\ \vdots \\ (x_{n,k} - x_{n\delta,k}) \end{bmatrix} \end{aligned}$$

The control law (5) with (6), which is referred to as the inverse optimal control law, optimizes the cost functional (2). Consequently, by considering $V(x_k)$ as in (6), control law (5) takes the following form:

$$\begin{aligned} u_k^* &= abs\left(-\frac{1}{4} R^{-1} g^T(x_k) \frac{\partial z_{k+1}^T P z_{k+1}}{\partial z_{k+1}} \right) \\ &= abs\left(-\frac{1}{2} \left(R + P_2(x_k) \right)^{-1} P_1(x_k, x_{\delta,k}) \right) \end{aligned} \quad (7)$$

with

$$P_1(x_k, x_{\delta,k}) = \begin{cases} g^T(x_k) P \left(f(x_k) - x_{\delta,k+1} \right) \\ \quad \text{for} \quad f(x_k) \succeq x_{\delta,k+1} \\ \\ g^T(x_k) P \left(x_{\delta,k+1} - f(x_k) \right) \\ \quad \text{for} \quad f(x_k) \preceq x_{\delta,k+1} \end{cases} \quad (8)$$

and

$$P_2(x_k) = \frac{1}{2} g^T(x_k) P g(x_k) \quad (9)$$

Moreover, with (6) as a CLF, this control law is inverse optimal in the sense that minimizes the cost functional (2). $P_1(\bullet)$ and $P_2(x_k)$ are positive definite and symmetric matrices; thus, the existence of the inverse in (7) is ensured.

III. Neural Model and Inverse Optimal Control

In this section a brief description of the neural model and controller are given, however the reader can refer to [24] in order to obtain more details. First, a neural model identification is performed and a RMLP (Recurrent Multi-Layer Perceptron) is chosen. The structure selected is NNARX [37] (Neural Network AutoRegressive eXternal input); the input vector to the artificial neural network is defined as the regression vector of an AutorRegressive eXternal input linear model structure (ARX) [38].

Following all the procedure presented in [24], the neural network implemented as a predictor form is:

$$\widehat{y}_{k+1} = S(\phi_k, w) + w' u_k \quad (10)$$

$$e_k = y_k - \widehat{y}_k \quad (11)$$

where w is the vector containing the adjustable parameters and w' is a fixed weight vector for inputs, which is used to ensure controllability of the neural model [39] and e_k is

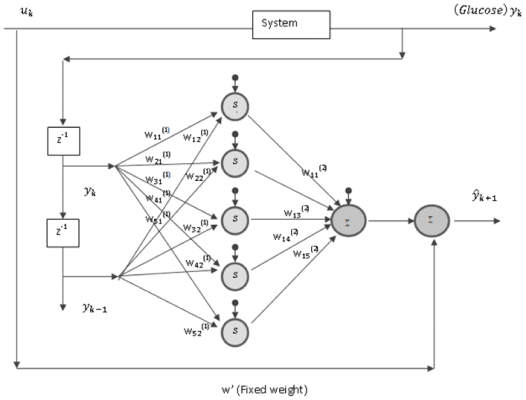

Fig. 1. Structure of the RMLP for glucose level modeling.

the prediction error, which includes all the effects produced by the neural network approximation, external disturbances, and plant parameter variations. As defined, (10) constitutes a RMLP neural network.

The RMLP used in this work contains sigmoid units only in the hidden layer; the output layer is a linear one. The sigmoid function $S(\bullet)$ is defined as

$$S(\varsigma) = \frac{1}{1+\exp(-\beta\varsigma)}, \beta > 0 \tag{12}$$

where ς is any real value variable. Finally, the neural network (10) becomes:

$$\hat{y}_{k+1} = \sum_{i=0}^{5} w_{1i}^{(2)} v_i \ + w' u_k \ \text{ with } v_0 = +1 \tag{13}$$

where

$$v_i = \left[S\left(\sum_{j=0}^{2} w_{ij}^{(1)} x_j \right) \right] \quad \text{with} \quad x_0 = +1. \tag{14}$$

Fig. 1 shows the structure of the RMLP for modeling of glucose level; it has 5 neurons in the hidden layer, with logistic activation functions (12), and the output layer is composed by one neuron, with a linear activation function. The initial values for the covariance matrices (R, Q, P) are $R_0 = Q_0 = P_0 = 10000$. The identification is performed on-line for each patient (male and female) using an EKF-learning algorithm in a series-parallel configuration. The EKF determines the optimal weight values which minimize the prediction error at every step; using these new new weights the covariance matrices are updated.

According to Fig. 1, $x_{1,k} = y_{k-1}$ and $x_{2,k} = y_k$, then

$$\begin{aligned} x_{1,k+1} &= y_k \\ x_{1,k+1} &= x_{2,k} \\ x_{2,k+1} &= y_{k+1} \\ x_{2,k+1} &= \hat{y}_{k+1} + \varepsilon \end{aligned}$$

In order to obtain a representation for control purposes as (1), the neural model (13) can be represented using state space variable as follows:

$$x_{1,k+1} = f_1(x_k) \tag{15}$$

$$x_{2,k+1} = f_2(x_k) + g(x_k)\, u(x_k) \tag{16}$$

$$\hat{y}_k = x_{2,k}$$

$$\begin{bmatrix} f_1(x_k) \\ f_2(x_k) \end{bmatrix} = \begin{bmatrix} x_{2,k} \\ \hat{y}_{k+1} \end{bmatrix}$$

$$g(x_k) = w'$$

where $x_{1,k+1}$ and $x_{2,k+1}$ are glucose levels, and u_k is the insulin dose.

IV. A Kernel-Based Regularization-Learning Algorithm

Blood glucose (BG) prediction has been focused upon for more than a decade and the subject of intensive multidisciplinary research. The most recent advances in BG prediction are based on the observation that pure data-driven algorithms lead to more clinically accurate results than the ones based on physiological models or a combination of both. In this framework, the problem can be stated as the function reconstruction problem from given noisy data. Assume that at the time moment $t = t_k$ we are given m preceding estimates $x_{BG_k}, x_{BG_{k-1}}, \ldots, x_{BG_{k-m+1}}$ of a patient's BG concentration sampled at the time moments $t_k > t_{k-1} > \ldots > t_{k-m+1}$ within the sampling horizon $SH = t_k - t_{k-m+1}$. The goal is to construct a predictive algorithm that uses these available measurements and possibly some additional information about therapeutically valuable factors to predict a BG concentration as a function of time $\hat{y}_{BG} = \hat{y}_t$ for T subsequent future time moments $t_{k+1}, \ldots, t_{k+T}$ within the prediction horizon $PH = t_{k+T} - t_{k+1}$ such that $t_{k+1} < \ldots < t_{k+T}$.

The kernel-based adaptive regularized learning (KAR) algorithm [25], considered in this paper, has both shown to outperform state-of-the-art prediction algorithms, and demonstrated high predictive accuracy in extensive clinical studies with more than 90 patients across Europe. The algorithm performance was especially robust for short-term (up to 40 min) predictions for patients with high glucose variability, including a significant risk of hypoglycemia.

In general terms, the KAR predictor extrapolates glucose values from a small number of glucose measurements made before the moment of a prediction. To be more precise, using the classical results of regularization theory [40], the KAR predictor is constructed as

$$\hat{y}_t = \sum_{i=k-m+1}^{k} c_i^{\lambda} K(t, t_i), \tag{17}$$

where K, a symmetric positive-definite function, uniquely determines a Reproducing Kernel Hilbert Space, in which

the extrapolation is performed. A real vector of coefficients $\mathbf{c}^{\lambda} = (c^{\lambda}_{k-m+1}, \ldots, c^{\lambda}_{k})$ is defined as

$$\mathbf{c}^{\lambda} = (\lambda m \mathbb{I} + \mathbb{K})^{-1} \mathbf{x}_{BG},$$

with $\mathbb{I}$ a unit matrix of the size $m \times m$, $\mathbb{K} = \{(K(t_j, t_i))\}^{0}_{i\ j=k-m+1}$ is the Gram matrix, and $\mathbf{x}_{BG}$ is the vector of a patient's past BG concentration (see [25] for further details).

In order to construct predictor (17) two important issues have to be addressed: how does one choose an adequate functional space, characterized by a symmetric positive-definite function K, called the kernel, and how does one choose the so-called regularization parameter λ.

The KAR algorithm addresses both issues and allows for the construction of the fully adaptive, flexible and accurate BG predictor. Construction of the algorithm consists of two separate stages performed by two learning machines: prediction setting stage (can be performed offline and only once) and prediction execution stage. During the first stage, the so-called main learning machine is trained on a specific data pool of measured physiological states in choosing adequate functional space, where the extrapolation will be made and from which an adequate extrapolating function may be selected. To be more specific, a non-linear relationship between given data segments as input and the best kernel and the regularization parameter values as output is created. This relationship is constructed by employing a data-driven regularization algorithm, e.g., by minimizing an error function expressed in terms of the Tikhonov-type functional which is minimized over a Reproducing Kernel Hilbert Space. The error function is given in terms of difference between predicted and actual blood glucose values.

As the outcome of the first stage, a non-linear relationship between the best kernels, the regularization parameters and the corresponding input data segments from the training set is constructed. During the second stage, a supervised learning machine is trained to construct a function from a given functional space. The machine presents a future glucose profile and is constructed by a data-driven regularization algorithm performed in the space suggested by the main machine.

To be more specific, during this stage of the prediction process, the trained non-linear relationship between data segments of the training set and desired parameters created in the main learning machine is used to determine the kernel and the regularization parameter for the final kernel to be used to construct the predictor of the form (17). These parameters are specific to the data, but need not be trained specific to a patient, i.e., the prediction setting stage can be employed independently of the individual user.

In addition to the superior performance, the KAR algorithms exhibits several attractive features: it is portable from individual to individual; does not require any readjustment; it produces prediction in the form of a function describing a future glucose profile, which allows more precise alarm / alert features to be incorporated. Furthermore, the algorithm works well on the data with essential time gaps in measurements, which makes it robust against temporary malfunctions in BG measurement systems.

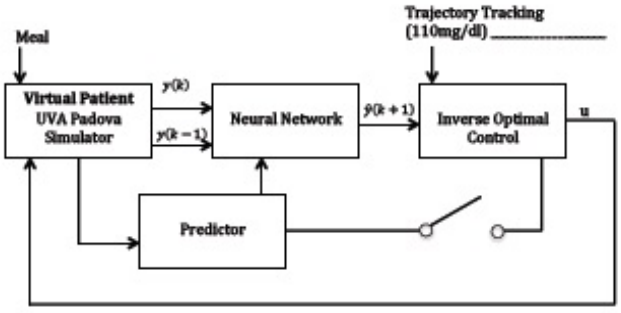

Fig. 2. Closed loop diagram for the control law combine with the predictor.

V. Simulation Results

In this section, simulation results are presented. Fig. 2 is a block diagram which portrays how the virtual patient (T1DMS), is connected to the on-line neural identifier, then, the blood glucose levels obtained from the virtual patient are used to predict the blood glucose level 20 minutes ahead with the KAR algorithm implemented as a predictor. The virtual patient uses as inputs the day's meals and the subcutaneous insulin calculated by the inverse optimal control law; then the on-line neural identifier captures the dynamics of the virtual patient. The model determined by the neural identifier is used to calculate the inverse optimal control law. However, the activation of the control law depends on the predictor. If the blood glucose level obtained by the predictor is less than 110mg/dl the control law is turned off; moreover, if the blood glucose level calculated by the predictor is equal or higher than 110mg/dl the control law is activated. The insulin calculated by the control law goes through the virtual patient, to supply the subcutaneous insulin dose, and to the neural model. The desired trajectory $(x_{\delta,k})$ is fixed to a value of 110 mg/dl. Simulations are implemented using Matlab [1].

A. First Scenario: Bolus Insulin Treatment 5 Days

It is very common for T1DM patients to use multiple-daily insulin injections. In this first scenario a simple bolus calculator (BC) (18) is used in order to estimate the insulin doses delivered to reach post-meal BG target for 10 different patients.

$$\textit{Insulin} = \frac{Carbs}{CIR} + \frac{BG_{\text{current}} - BG_{\text{target}}}{ISF} \qquad (18)$$

where *Carbs* is the amount of carbohydrates consumed during a meal, CIR is the Carbohydrate-to-Insulin Ratio,

[1]It is a trade mark of the MathWorks, Inc.

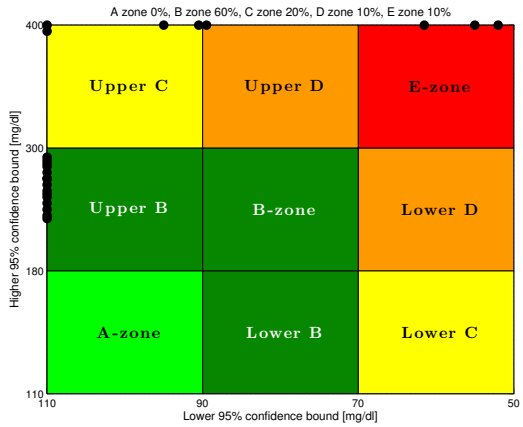

Fig. 3. CVGA for 10 different patients regulated using bolus insulin treatment with meals during 5 days.

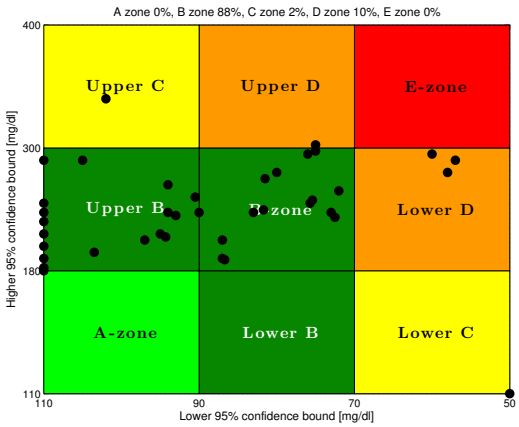

Fig. 4. CVGA for 10 different patients controlled using inverse optimal control strategy for non-linear systems via CLF.

BG_{current}, BG_{target} are current and target blood glucose (BG) levels, and ISF is the Insulin Sensitivity. The simulation starts at 12:00am and patients have three different meals; at 8:00am, 1:00pm and 6:00pm with 50, 40 and 30 grams of carbohydrates respectively during one day.

Control-variability grid analysis [26] is used to present all the results. Table 1 presents all the boundaries of the zones in the CVGA. The meanings of each zone according to [26] are: accurate control for A zone, benign deviations into hypoglycemia for Lower B zone, benign control deviations for B zone, benign deviations into hyperglycemia for upper B zone, over correction of hyperglycemia for lower C zone, over correction of hypoglycemia for upper C zone, failure to deal with hypoglycemia upper C zone, failure to deal with hypoglycemia for lower D zone and erroneous control E zone. A zone is the safest and E zone is the most dangerous zone.

A	X Range 110-90mg/dl and Y range 110-180mg/dl
Lower B	X=90-70mg/dl and Y=110-180mg/dl
B	X=90-70mg/dl and Y=180-300mg/dl
Upper B	X = 110–90 mg/dl, Y = 180–300 mg/dl
Lower C	X $<$ 70 mg/dl, Y = 110–180 mg/dl
Upper C	X = 110–90 mg/dl, Y $>$ 300 mg/dl
Lower D	X $<$ 70 mg/dl, Y = 180–300 mg/dl
Upper D	X = 90–70 mg/dl, Y $>$ 300 mg/dl
E	X $<$ 70 mg/dl and Y $>$ 300 mg/dl

The CVGA for this experiment is shown in Fig. 3; the summary outcome is A=0%, B=60%, C=20%, D=10% and E=10%, A+B=60% and C+D+E=40%.

As it can be seen, in Fig. 3, even when a bolus treatment is supplied to each patient every time they have a meal, this technique is not enough to regulate their blood glucose level. Moreover, there is a 10% in the E zone, indicating complete failure of the treatment. Trying to regulate blood glucose levels of patients using this technique entails complications.

B. Second Scenario: Control Insulin Treatment 5 Days

A second scenario set with the same meals and hours as the first scenario is tested using inverse optimal control strategy for non-linear systems via CLF explained in section 2. This experiment is done with the aim to compare it with the first scenario and show how the blood glucose level of the patients can be better regulated using a control technique. The control law is tuned for each patient in order to obtain the best results. The CVGA summary outcome applying inverse optimal control via CLF in Fig. 4 shows a 0% in A zone, 88% in zone B, 2% in zone C and 10% for zone D and E, A+B=88%, C+D+E=12%.

In the first scenario A+B=60%, however using inverse optimal control via CLF this percentage is increased to 88%. C+D+E percentage in the first scenario was 30% compared with only 12% in the second scenario. Of that 30%, 10% was in E zone, which is dangerous for a patient. Comparing both results suggests that using a control technique is safe than only using insulin bolus treatment in T1DM patients.

C. Third Scenario: Control Insulin Treatment Plus Predictor 5 Days

In this sub-section the inverse optimal control via CLF in combination with a KAR algorithm used as a predictor are tested in the third scenario. The simulation start time and meals were the same as the preceding scenarios, it run for 5 days and the control law tuned for each patient as the third scenario. The predictor gives the blood glucose level of the patients 20 minutes ahead. Then, as Fig. 2 shows, the control law activation depends on the predictor value. If the predictor value is less than 110mg/dl the control law remains unactive, however, if the blood glucose level predicted is 110mg/dl or higher the control law is activated

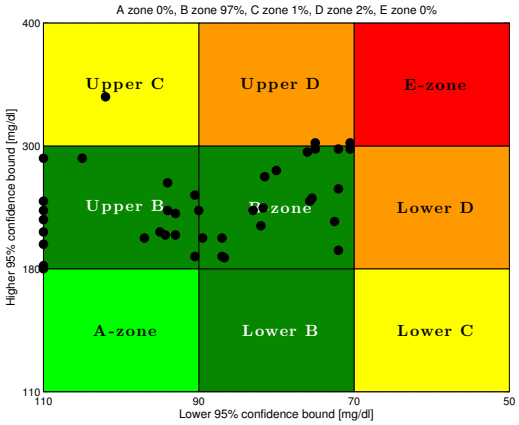

Fig. 5. CVGA for 10 different patients controlled using inverse optimal control strategy for non-linear systems via CLF in combination with a kernel-based regularization learning algorithm.

and insulin is administrated to the virtual patient. The advantage of using a predictor instead of an on/off controller is that a hypoglycemia period can be identified in advance time and deactivating the controller can be avoided. Fig. 5 shows results for this experiment. It is worth noting that failure to correct hypoglycemia has been eliminated with the combination of the predictor and the controller. As well as B zone increases from 88% to 97%, C zone decreases from 2% to 1% and D zone decreases from 10% to 2%. These results demonstrate the value of the predictor for the regulation of blood glucose levels in T1DM patients.

VI. CONCLUSIONS

This paper tested a neural inverse optimal control via control Lyapunov function (CLF) in combination with a kernel-based regularization-learning algorithm with the University of Virginia/Padova Simulator. Three different scenarios are shown; the first one used a simple bolus calculator for bolus insulin treatment; with this method only 60% of patients were well regulated. A second scenario showed that the control technique outperforms a bolus treatment. Inverse optimal control via CLF supports good results for patients, nevertheless, it still fail to eliminate hypoglycemia. Thus, a kernel-based regularization learning algorithm is used as a predictor linked up with the inverse optimal control via CLF in order to prevent hypoglycemia periods. Simulation results from the fourth scenario showed the effectiveness of this combination. Simulation results also showed the success of the proposed RNN for deriving an affine dynamical mathematical model for the T1DM, for the patient response to meals (unknown disturbance) and subcutaneous insulin infusion (system input).

VII. ACKNOWLEDGMENT

The first author acknowledges the support of the UC-Mexus/Conacyt Fellowship, the National Biomedical Computation Resource (NIH P41 GM103426).

REFERENCES

[1] Harris M, Zimmet P, Classification of diabetes mellitus and other categories of glucose intolerance. In Alberti K, Zimmet P, Defronzo R, editors. International Textbook of Diabetes Mellitus. Second Edition. Chichester: John Wiley and Sons Ltd; 1997. pp. 9-23.

[2] Levine R. Insulin action: 1948–80. Diabetes Care, 1981, vol. 4, pp. 38–44.

[3] The Diabetes Control and Complications Trial Research Group. 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N. Engl. J. Med., 1993, vol. 329, pp. 977-986.

[4] Bakatselos SO,“ Hypoglycemia unawareness”. *Diabetes Res Clin Pract*, 2011, vol. 15, no. 93, pp. S92–6

[5] J. S. Skyler, “Continuous subcutaneous insulin infusion—an historical perspective”, *Diabetes Technology & Therapeutics*, 2010, vol. 12, no. 1, pp. s5-s9.

[6] Guidance for Industry and Food and Drug Administration Staff, (November, 2012): The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems. [Online]. Available: http://www.fda.gov/downloads/MedicalDevices / DeviceRegulationandGuidance /GuidanceDocuments/UCM259305. pdf.

[7] B. P. Kovatchev, M. Breton, C. D. Man, C. Cobelli, “In silico preclinical trials: a proof concept in closed-loop control of type 1 diabetes”, *Journal of Diabetes Science and Technology*. 2009, vol. 3, no. 3, pp. 44-55.

[8] C. D. Man, D. M. Raimondo, R. A. Rizza, C. Cobelli, “Gim simulation software of meal glucose-insulin model”, *Journal of Diabetes Science and Technology*. 2007, vol. 1, no. 3, 323-330.

[9] C. C. Palerm, “Physiologic insulin delivery with insulin feedback: A control systems perspective”, *Computer Methods and Programs in Biomedicine*. 2011, vol. 102, no. 2, 130-137.

[10] Hyunjin Lee 1, B.Wayne Bequette, “A closed-loop artificial pancreas based on model predictive control: Human-friendly identification and automatic meal disturbance rejection”, *Biomedical Signal Processing and Control*, 2009, vol. 4, pp. 347–354.

[11] G. M. Steil, A. E. Panteleon, and K. Rebrin, “Closed-loop insulin de delivery the path to physiological glucose control”, *Advanced Drug Delivery Reviews*. 2004, vol. 56, pp. 125-144.

[12] M. W. Percival, E. Dassau, H. Zisser, L. Jovanovic, F. Doyle, “Practical approach to design and implementation of a control algorithm in an artificial pancreatic beta cell”, *Industrial & Engineering Chemistry Research*. 2009, vol. 48, pp. 6059-6067.

[13] L. Magni, M. Forgione, C. Toffanin, C. D. Man, B. Kovatchev, G. De Nicolao, C. Cobelli, “Run-to-run tuning of model predictive control for type 1 diabetes subjects, in silico trial”, *Journal of Diabetes Science and Technology*. 2009, vol. 3, pp. 1091-1098.

[14] M. W. Percival, H. Zisser, L. Jovanovic and F. J. Doyle, “Closed-loop control and advisory mode evaluation of an artificial pancreatic β cell: use of proportional-integral-derivative equivalent model-based controllers”, *Journal of Diabetes Science and Technology*, 2008, vol. 2, no. 4, pp. 636-644.

[15] Chiara Toffanin, Mirko Messori, Federico Di Palma, Giuseppe De Nicolao, Claudio Cobelli, and Lalo Magni, “Artificial Pancreas: Model Predictive Control Design from Clinical Experience”, *Journal of Diabetes Science and Technology*, 2013, vol. 7, no. 6, pp. 1470-1483.

[16] L. Magni, D.M. Raimondo, C. Dalla Man, G. De Nicolao, B. Kovatchev, C. Cobelli, “Model predictive control of glucose concentration in type I diabetic patients: An in silico trial”, *Biomedical Signal Processing and Control*, 2009, vol. 4, pp. 338-346.

[17] C. Ellingsen, E. Dassau, H. Zisser, B. Grosman, M. W. Percival, L. Jovanovič, F. J. Doyle III, “Safety constraints in an artificial pancreatic β cell: an implementation of model predictive control with insulin on board”, *Diabetes Technology Society*, 2009, vol. 3, no. 3, pp. 536-544.

[18] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M.Massi-Benedetti, M. Orsini-Federici, T. R. Pieber, H. Schaller, L. Schaupp, T. Vering, and M. Wilinska, “Non-linear model predictive control of glucose concentration in subjects with type 1 diabetes”, *Physiol. Meas*. 2004, vol. 25, pp. 905-920.

[19] Y. Wang, E. Dassau, F. J. Doyle, "Closed-loop control of artificial pancreatic β- cell in type 1 diabetes mellitus using model predictive iterative learning control", *IEEE Transactions on Biomedical Engineering*. 2010, vol. 57, no. 2, pp. 211-219.

[20] Ali, Sk.F., & Padhi, R. (2009). "Optimal blood glucose regulation of diabetic patients using single network adaptive critics". *Optimal Control Applications and Methods*, 2011, vol. 32, pp. 196-214.

[21] L. Kovács, B. Kulcsár, A. György, and Z. Benyó, "Robust servo control of a novel type 1 diabetic model", *Optimal Control Applications and Methods*. 2010, vol. 32, pp. 215-238.

[22] Quiroz, G., Flores-Gutiérrez, C.P. & Femat, R. (2011). "Suboptimal H_∞ hyperglycemia control on T1DM accounting biosignals of exercise and nocturnal hypoglycemia". *Optimal Control Applications and Methods,* 2011*,* vol. 32, pp. 239-252.

[23] R. Femat, E. Ruiz-Velázquez and G. Quiroz, G., "Weighting restriction or intravenous insulin delivery on T1DM patient via H_∞ control", *IEEE Transactions on Automatization Science and Engineering*, 2009, vol. 6, pp. 239-247.

[24] Blanca S. Leon, Alma Y. Alanis, Edgar N. Sanchez, Fernando Ornelas-Tellez, Eduardo Ruiz-Velazquez, "Neural inverse optimal control applied to type 1 diabetes mellitus patients, *Analog Integr Circ Sig Process*, ,2013, vol. 73, no. 3, pp. 343-352.

[25] V. Naumova, S.V. Pereverzyev, S. Sivananthan, "A meta-learning approach to the regularized learning—Case study: Blood glucose prediction", *Neural Networks*, 2012, Vol. 33, pp. 181-193.

[26] Lalo Magni, Davide M. Raimondo, Chiara Dalla Man, Marc Breton, Stephen Patek, Giuseppe De Nicolao, Claudio Cobelli, and Boris P. Kovatchev, "Evaluating the Efficacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis", *Journal of Diabetes Science and Technology*, 2008, vol. 2, no. 4, pp. 630-635.

[27] C. D. Man, R. A. Rizza, C. Cobelli, "Meal simulation model of the glucose-insulin system", *IEEE Transactions on Biomedical Engineering*. 2007, vol. 54, no. 10, pp. 1740-1749.

[28] P.Colmegna, R. S. Sanchez Pena, E. Dassau, F. J. Doyle III, "Reducing Risks in Type 1 Diabetes Using H_∞ Control", *IEEE Transactions on Biomedical Engineering*. 2014, vol. 61, no, 12, pp. 2939-2947.

[29] K. Zarkogianni, A. Vazeou, S.G. Mougiakakou, A. Prountzou, K.S. Nikita, "An Insulin Infusion Advisory System Based on Autotuning Nonlinear Model-Predictive Control", *IEEE Transactions on Biomedical Engineering*. 2011, vol. 58, no. 09, pp. 2467-2477.

[30] M. Messori, M. Ellis, C. Cobelli, P.D. Christofides, L. Magni, "Improved Postprandial Glucose Control with a Customized Model Predictive Controller", *Proceedings of the American Control Conference*, Chicago, IL, USA, 2015, pp. 5108-5115.

[31] R. A. Freeman and P. V. Kokotović, *Robust Nonlinear Control Design: State-Space and Lyapunov Techniques*. Cambridge, MA, USA: Birkhauser Boston Inc., 1996.

[32] D. E. Kirk, *Optimal Control Theory: An Introduction. Englewood Cli s*, NJ, USA: Prentice-Hall, 1970.

[33] F. L. Lewis and V. L. Syrmos, *Optimal Control*. New York, NY, USA: John Wiley & Sons, 1995.

[34] T. Basar and G. J. Olsder, *Dynamic Noncooperative Game Theory*, 2nd ed. New York, NY, USA: Academic Press, 1995.

[35] T. Ohsawa, A. M. Bloch, and M. Leok, "Discrete Hamilton-Jacobi theory and discrete optimal control", *Proceddings of the 49th IEEE Conference on Decision and Control* (CDC), Atlanta, Ga, USA, Dec. 2010, pp. 5438-5443.

[36] A. Al-Tamimi and F. L. Lewis, "Discrete-time nonlinear HJB solution using approximate dynamic programming: Convergence proof", *IEEE Transactions on Systems, Man, Cybernetics-Part B*, vol. 38, no. 4, pp. 943-949, 2008.

[37] M. Norgaard , N. K. Poulsen , and O. Ravn, "Advances in Derivative-Free State Estimation for Nonlinear Systems", *Technical Report IMM-REP-1988-15* (revised edition), Technical University of Denmark (2000).

[38] E. N. Sanchez, A. Y. Alanis and J. J. Rico, "Electric load demand prediction using neural networks trained by kalman filtering", *Proceedings of the IEEE International Joint Conference on Neural Networks*, vol. 4 Budapest, Hungray, July 2004, pp. 2771 - 2775.

[39] F. Ornelas, E. N. Sanchez and A. G. Loukianov "Discrete-time inverse optimal control for nonlinear systems trajectory tracking", *Proceedings of the 49th IEEE Conference on Decision and Control*, vol. 1, San Diego, California, USA, Dec. 2009, pp. 923–924.

[40] G. Wahba, *Spline Models for Observational Data*, vol. 59 of Series in Applied Mathematics*,* CBMS-NSF Regional Conf., SIAM, 1990.